

CLAIMS

We claim:

1. A targeting construct comprising:
 - (a) a first polynucleotide sequence homologous to a secreted protein gene;
 - (b) a second polynucleotide sequence homologous to the secreted protein gene;
 - and
 - (c) a selectable marker.
2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.
3. A method of producing a secreted protein gene targeting construct, the method comprising:
 - (a) providing a first polynucleotide sequence homologous to a secreted protein gene;
 - (b) providing a second polynucleotide sequence homologous to the secreted protein gene;
 - (c) providing a selectable marker; and
 - (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.
4. A method of producing a secreted protein gene targeting construct, the method comprising:
 - (a) providing a polynucleotide comprising a first sequence homologous to a first region of a secreted protein gene and a second sequence homologous to a second region of a secreted protein gene;
 - (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.
5. A cell comprising a disruption in a secreted protein gene.
6. The cell of claim 5, wherein the cell is a murine cell.
7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.
8. A non-human transgenic animal comprising a disruption in a secreted protein gene.
9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a secreted protein encoding gene, the method comprising:
- (a) introducing the targeting construct of claim 1 into a cell;
 - (b) introducing the cell into a blastocyst;
 - (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
 - (d) breeding the chimeric mouse to produce the transgenic mouse.
11. A method of identifying an agent that modulates the expression of a secreted protein encoding gene, the method comprising:
- (a) providing a non-human transgenic animal comprising a disruption in the secreted protein encoding gene;
 - (b) administering an agent to the non-human transgenic animal; and
 - (c) determining whether the expression of the secreted protein encoding gene in the non-human transgenic animal is modulated.
12. A method of identifying an agent that modulates the function of a secreted protein encoded by a secreted protein encoding gene, the method comprising:
- (a) providing a non-human transgenic animal comprising a disruption in the secreted protein encoding gene;
 - (b) administering an agent to the non-human transgenic animal; and
 - (c) determining whether the function of the secreted protein in the non-human transgenic animal is modulated.
13. A method of identifying an agent that modulates the expression of a secreted protein gene, the method comprising:
- (a) providing a cell comprising a disruption in the secreted proteingene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether expression of the secreted protein gene is modulated.
14. A method of identifying an agent that modulates the function of a secreted protein gene, the method comprising:
- (a) providing a cell comprising a disruption in the secreted protein gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether the function of the secreted protein gene is modulated.

15. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.
16. A transgenic mouse comprising a disruption in a secreted protein gene, wherein the transgenic mouse exhibits a behavioral abnormality.
17. The transgenic mouse of claim 17, wherein the transgenic mouse exhibits an anti-depressive condition.
18. The transgenic mouse of claim 18, wherein the anti-depressive condition is characterized by decreased time spent immobile in a tail suspension test, relative to a wild-type mouse.
19. A method of producing a transgenic mouse comprising a disruption in a secreted protein gene, wherein the transgenic mouse exhibits an anti-depressive condition, the method comprising:
 - (a) introducing a targeting construct specific for the secreted protein gene into a cell;
 - (b) introducing the cell into a blastocyst;
 - (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
 - (d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in the secreted protein gene.
20. A cell derived from the transgenic mouse of claim 17 or claim 20.
21. A method of identifying an agent that has an effect on depression, the method comprising:
 - (a) administering an agent to a transgenic mouse comprising a disruption in a secreted protein gene; and
 - (b) determining whether the agent has an effect on depression, wherein the effect on depression is measured in a behavioral test.
22. A method of identifying an agent that modulates expression of a secreted protein gene, the method comprising:
 - (a) administering an agent to a transgenic mouse comprising a disruption in the secreted protein gene; and

- (b) determining whether the agent modulates expression of the secreted protein gene in the transgenic mouse, wherein the agent has an effect on an anti-depressive condition.
23. A method of identifying an agent that modulates a behavior associated with a disruption in a secreted protein gene, the method comprising:
- (a) administering an agent to a transgenic mouse comprising a disruption in the secreted protein gene; and
 - (b) determining whether the agent has an effect on depression, wherein the effect on depression is measured in a behavioral test.
24. A method of identifying an agent that modulates the function of a secreted protein gene encoding a secreted protein, the method comprising:
- (a) providing a cell comprising a disruption in the secreted protein gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether the agent modulates the function of the secreted protein gene, wherein the agent modulates a phenotype associated with a disruption in the secreted protein gene.
25. The method of claim 25, wherein the phenotype comprises anti-depressant behavior.
26. A method of identifying an agent that has an effect on depression, the method comprising:
- (a) providing a secreted protein encoded by a secreted protein gene;
 - (b) contacting the secreted protein with an agent; and
 - (c) determining if the agent modulates the function of the secreted protein.
27. A method of identifying an agent that has an effect on depression, the method comprising:
- (a) providing a cell expressing a secreted protein gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether the agent affects the function of the secreted protein.
28. A method of identifying an agent that has an effect on depression, the method comprising:
- (a) providing a cell overexpressing a secreted protein gene;

- (b) contacting the cell with an agent; and
- (c) determining whether the agent affects the expression of the secreted protein gene.

29. The method of claim 28, wherein the agent decreases the expression of the secreted protein gene.
30. An agent identified by the method of claim 26, claim 27, or claim 28.
31. A method of treating depression, or ameliorating symptoms associated therewith, the method comprising administering to a patient in need a therapeutically effective amount of an agent that modulates expression of a secreted protein gene.
32. A method of treating depression, or ameliorating symptoms associated therewith, in a patient in need, the method comprising administering to a patient in need a therapeutically effective amount of an agent that inhibits the expression or activity of a protein encoded by a secreted protein gene.
33. A method of treating depression, or ameliorating symptoms associated therewith, in a patient in need, the method comprising administering an agent that modulates the activity of a secreted protein encoded by a secreted protein gene.
34. The method of claim 33, wherein the agent is an antagonist of the secreted protein.
35. The method of claim 34, wherein the antagonist is an antibody.